

Flow Reaction

Continuous-Flow Dynamic Kinetic Resolution of Racemic Alcohols by Lipase–Oxovanadium Cocatalysis

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Abstract: A continuous-flow dynamic kinetic resolution of racemic secondary alcohols was carried out using a single column reactor packed with a mixture of immobilized lipase and an immobilized oxovanadium species, VMPS4. As a result, optically pure esters were produced in 88–92 % yields. Problems encountered in this study were overcome by using fillers that efficiently

maintained the initial distribution of the catalysts in the reactor and by using a packing method in which the mixing ratio of the two catalysts was varied in a stepwise fashion. The flow process led to an increased turnover number of each catalyst compared to those of batch reactions.

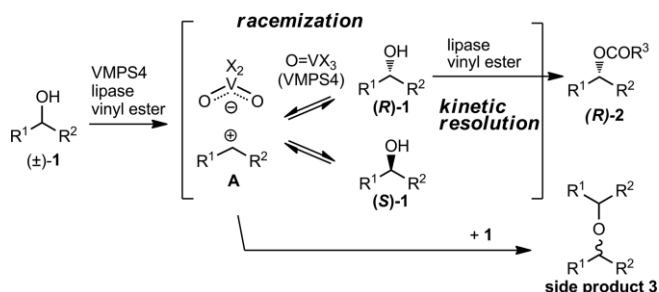
Introduction

Flow chemistry has drawn increasing attention in the last few decades.^[1] In particular, the application of flow reactors for continuously running processes in the presence of heterogeneous catalysts has emerged with great potential.^[1,2] The use of packed-bed reactors, for example, improves the turnover numbers and lifetimes of the catalysts by avoiding their tedious recovery for reuse as in case of batch reactions that requires additional handling to set up the next reaction. Additionally, the continuous-flow processes generally present advantages over batch procedures, such as better mass and heat transfer, improved safety profiles, easier work-up and as well as the accurate control of temperature, pressure and reaction time. Thus, continuous-flow processes have higher productivity and reproducibility than the batch reactions, and are also favorable for automation and scale-up.^[1–3]

Lipases, a class of hydrolases, exhibit high catalytic activity and enantioselectivity even in organic solvents and have been widely used for kinetic resolution (KR) of racemic alcohols. However, KR has an inherent limitation: the maximum yield of each product is 50 %. To overcome this problem, dynamic kinetic resolution (DKR) has been developed by combining lipase-catalyzed KR with the in situ racemization of the less reactive enantiomers in a single flask, thus allowing the conversion of

racemic alcohols into optically pure esters in up to 100 % yield.^[4] For rapid racemization, an additional catalyst is employed, which consists of, for example, Ru(II), Ir(III), and Fe(II) complexes or Pd(0) supported on matrices,^[4,5] aluminum compounds,^[6] oxovanadium compounds,^[7] strong acids supported on solid materials,^[8] and inorganic solid acids such as zeolites.^[9] Some reagents, such as Ru(II) complexes and the aluminum compounds, have been proved to be relatively tolerant to lipases, whereas other catalysts require separation from lipases to prevent mutual inactivation.

We also invented oxovanadium compounds for the racemization of benzylic, allylic, and propargylic alcohols and applied them to the DKR of these racemic alcohols in a batch system.^[10] Among our DKR methods, the use of our original catalyst, VMPS4, in which oxovanadium species were covalently bound to the inner surface of mesoporous silica, dramatically enhanced the catalyst compatibility with immobilized lipases (Scheme 1).



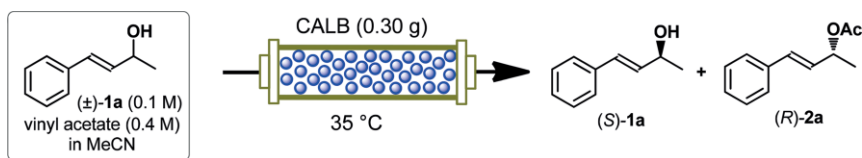
Scheme 1. Lipase–oxovanadium cocatalyzed dynamic kinetic resolution of racemic alcohols **1**.

A pioneering work on the lipase–oxovanadium cocatalyzed continuous-flow DKR of racemic *sec*-alcohols was reported by Poppe et al. using a reactor alternately connected with catalyst cartridges containing *Candida antarctica* lipase B and V₂O₄.^[7c] Another continuous-flow DKR system reported by Souza et al.

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Table 1. Effects of flow rate on the continuous-flow KR of (\pm)-**1a** using a column reactor packed with CALB.

Entry	Flow rate [mL/min]	Residence time [min]	Conv. ^[a] [%]	(<i>R</i>)- 2a , ee ^[b] [%]	<i>E</i> value ^[c]
1	0.10	7.5	46	99	>200
2	0.05	15	50	98	>200
3	0.03	20	51	97	>200
4	0.02	30	51	96	>200

[a] Conversion was determined by ¹H NMR analysis of the crude product obtained from 2 mL of the eluent collected after the system had reached a steady state. [b] Optical purity was determined by HPLC using a chiral column, Daicel CHIRALPAK AD-3 (4.6 mm × 250 mm). [c] See Ref.^[14]

used a single column reactor in which four layers of *Candida antarctica* lipase B and three layers of VOSO₄·*n*H₂O were alternately arranged and physically separated by a thin cotton layer.^[7a,7b] In both cases, the separation of the oxovanadium compounds from the lipase was needed because of their incompatibility with each other. In contrast, taking the advantages of excellent compatibility between VMPS4 and lipases,^[10] we applied our DKR process to a continuous-flow system using a single column reactor packed with a complete mixture of these two catalysts. However, we realized that our flow system, in which two different reactions, viz., racemization and kinetic resolution, proceeded simultaneously, had critical problems that had not been observed in our previous batch reactions.^[10] We speculate that similar problems could arise in other continuous-flow reactions using column reactors homogeneously packed with multiple solid catalysts. In this paper, we report our strategy to overcome these problems. Furthermore we report the substrate scope of our flow DKR and the results of continuous-flow operation over 3 days.

Results and Discussion

First, we carried out preliminary studies on the application of our batch reactions^[10] to continuous-flow KR^[11] using a column reactor^[12] which was packed with 0.30 g of *Candida antarctica* lipase B (CALB) immobilized on an acrylic resin (commercial name: Novozym 435 or Chirazyme L-2 C4). During the reaction, a solution of (\pm)-**1a** (0.1 M) and vinyl acetate (0.4 M) in MeCN was pumped through the reactor at 35 °C. The flow rate of the substrate solution was changed in a stepwise manner (Table 1), and it was found that the conversion of the reaction reached 50 % when the flow rate was 0.05 mL/min or lower, which secured a residence time^[13] of 15 min or more. In all cases, ester (*R*)-**2a** was obtained with 96–99 % ee, and the corresponding *E* values^[14] were greater than 200.

We then investigated the DKR of (\pm)-**1a** and its *para*-methoxy derivative (\pm)-**1b** using a column reactor containing a mixture of CALB and VMPS4 (vanadium content: 0.2 mmol/g); however, we noticed that the initial homogeneous distribution of the two catalysts in the column reactor was gradually lost during operation, resulting in a decrease in the efficiency of our collaborative catalysis process. This change in the catalyst distribution

was caused by the significantly different particle sizes of CALB (0.35–0.70 mm) and VMPS4 (0.030–0.050 mm) so that the smaller VMPS4 particles moved downstream along the flow. To solve this problem, filler particles were examined to maintain the initial distribution of the catalysts in the reactor. Thus, CALB (0.30 g), VMPS4 [100 mg (0.02 mmol of vanadium amount) for **1a** and 20 mg (0.004 mmol of vanadium amount) for **1b**], and filler particles were mixed well, and the mixture was poured into the column reactor. Then, a solution of either (\pm)-**1a** (0.1 M) or (\pm)-**1b** (0.1 M) with vinyl acetate (0.4 M) in MeCN was pumped into the reactor at 35 °C at a flow rate of 0.03 mL/min. Note that the amount of each filler was selected to adjust the residence time to 30 min (for details of the effects of the residence time, see Table S1 in Supporting Information). Of the tested fillers, Celite (particle size 0.020–0.10 mm) and silica gel (particle size 0.040–0.050 mm) were found to be relatively efficient, yielding (*R*)-**2a** (ca. 80 % yield, 99 % ee) (Table 2, entries 1 and 2) and (*R*)-**2b** (ca. 70 % yield, 96–98 % ee) (entries 4 and 5); however, the slow downstream movement of VMPS4 was still observed in these cases. After further investigation, a more advantageous filler, DualPoreTM silica beads (particle size 0.020–0.063 mm),^[15] was discovered. Thus, a reactor was packed with a homogeneous mixture of CALB, VMPS4, and DualPoreTM silica beads, which were found to maintain their initial distribution for more than 3 days when running the process in a continuous-flow mode (vide infra). Fortuitously, this experimental setup also resulted in better consumption of **1** (Table 2, entries 3 and 6) than that using either Celite or silica gel as the filler. In addition, the use of DualPoreTM silica beads efficiently enhanced the racemization, giving the best yield of (*R*)-**2b** (Table 2, entries 4–6).

Another issue observed in our continuous-flow DKR was the formation of significant amounts of dimeric ethers **3a** and **3b**, which were generated by the reaction of a racemization intermediate, allyl cation **A**, with another molecule of **1** (Scheme 1).^[16] Similar problems were also reported in the flow DKR using other oxovanadium catalysts; however, no solution has been found yet.^[7] After extensive screening of the reaction conditions, we found that the use of a reactor packed in a stepwise manner with increasing ratio of VMPS4 to CALB in three layers, had a significant suppressing effect on the formation of **3b** (Table 3, compare entries 1 and 4, 2 and 5, and 3 and 7). In

Table 2. Effects of fillers on the continuous-flow DKR of (±)-**1a**, **b** using a reactor containing CALB and VMPS4.

Entry	1	VMPS4	Filler ^[a]	(R)-2	Ratio ^[b] [%]	ee ^[c] [%]	(S)-1	Ratio ^[b] [%]	ee ^[c] [%]	3
1	1a	100 mg	Celite ^[e] (0.30 g)	(R)- 2a	84	99	(S)- 1a	2	nd	3a 14
2	1a	100 mg	silica gel ^[f] (0.20 g)	(R)- 2a	82	99	(S)- 1a	5	nd	3a 13
3	1a	100 mg	DualPore silica ^[g] (0.10 g)	(R)- 2a	84	99	(S)- 1a	<1	nd	3a 16
4	1b	20 mg	Celite ^[e] (0.50 g)	(R)- 2b	71	97	(S)- 1b	28	91	3b 1
5	1b	20 mg	silica gel ^[f] (0.28 g)	(R)- 2b	74	96	(S)- 1b	22	88	3b 4
6	1b	20 mg	DualPore silica ^[g] (0.14 g)	(R)- 2b	87	98	(S)- 1b	4	28	3b 9

[a] The amount of the filler was selected to adjust the residence time to 30 min. [b] Molar ratio [%] of the compounds (R)-**2**, (S)-**1**, and **3** was determined by ¹H NMR analysis of the crude product obtained from 2 mL of the eluent collected after the system had reached a steady state. [c] Optical purity was determined by HPLC using a chiral column, Daicel CHIRALPAK AD-3 (4.6 mm × 250 mm). Nd: not determined. [d] The ratio was calculated on the basis of the alcohol moiety and corresponded to half this quantity based on the molar amount. [e] Kishida Chemical Co., Ltd., particle size: 0.020–0.10 mm. [f] Kanto Chemical Co., Inc., particle size: 0.040–0.050 mm, density: 0.49 g/mL. [g] DPS Inc., particle size: 0.020–0.063 mm, density: 0.16 g/mL.

addition, reducing the total ratio of VMPS4 to CALB suppressed the formation of **3b**, although the recovery of **1b** was gradually increased (Table 3, entries 4–7). On the other hand, the use of

a reactor packed in a stepwise decreasing ratio of VMPS4 to CALB produced (R)-**2b**, (S)-**1b**, and **3b** (Table 3, entry 8), whose molar ratio was similar to that obtained using the single layer

Table 3. Continuous-flow DKR of (±)-**1a**, **b** using a reactor with a ratio gradient of CALB and VMPS4.

(±)-**1a**: R = H
(±)-**1b**: R = OMe

vinyl acetate (0.4 M)
in MeCN

CALB (0.30 g)
VMPS4 (x g)
DualPore silica (y g)

1st layer 2nd layer 3rd layer

35 °C
residence time: 30 min
flow rate: 0.03 mL /min

(*R*)-**2a, b**

3a, b

Entry	(±)- 1	VMPS4	DualPore silica ^[a]	Ratio (w/w) of VMPS4/CALB		<i>(R)</i> - 2		<i>(S)</i> - 1		3		
				Total ratio	Ratio in each layer		Ratio ^[b] [%]	ee ^[c] [%]	Ratio ^[b] [%]	ee ^[c] [%]	Ratio ^[b,d] [%]	
1	(±)- 1b	61 mg	118 mg	0.20:1	one layer	(<i>R</i>)- 2b	78	98	(<i>S</i>)- 1b	<1	nd	3b 22
2	(±)- 1b	30 mg	135 mg	0.10:1	one layer	(<i>R</i>)- 2b	81	98	(<i>S</i>)- 1b	<1	nd	3b 19
3	(±)- 1b	15 mg	143 mg	0.05:1	one layer	(<i>R</i>)- 2b	70	98	(<i>S</i>)- 1b	15	30	3b 15
4	(±)- 1b	61 mg	118 mg	0.20:1	0.11:1 (1st), 0.17:1 (2nd), 0.33:1 (3rd)	(<i>R</i>)- 2b	88	97	(<i>S</i>)- 1b	<1	nd	3b 12
5	(±)- 1b	30 mg	135 mg	0.10:1	0.06:1 (1st), 0.10:1 (2nd), 0.14:1 (3rd)	(<i>R</i>)- 2b	91	98	(<i>S</i>)- 1b	<1	nd	3b 9
6	(±)- 1b	22 mg	139 mg	0.07:1	0.05:1 (1st), 0.07:1 (2nd), 0.10:1 (3rd)	(<i>R</i>)- 2b	88	98	(<i>S</i>)- 1b	4	0	3b 8
7	(±)- 1b	15 mg	143 mg	0.05:1	0.03:1 (1st), 0.05:1 (2nd), 0.07:1 (3rd)	(<i>R</i>)- 2b	89	98	(<i>S</i>)- 1b	6	22	3b 5
8	(±)- 1b	22 mg	139 mg	0.07:1	0.10:1 (1st), 0.07:1 (2nd), 0.05:1 (3rd)	(<i>R</i>)- 2b	77	98	(<i>S</i>)- 1b	4	74	3b 19
9	(±)- 1a	100 mg	98 mg	0.33:1	one layer	(<i>R</i>)- 2a	84	98	(<i>S</i>)- 1a	<1	nd	3a 16
10	(±)- 1a	100 mg	98 mg	0.33:1	0.17:1 (1st), 0.33:1 (2nd), 0.50:1 (3rd)	(<i>R</i>)- 2a	93	98	(<i>S</i>)- 1a	<1	nd	3a 7
11 ^[e]	(±)- 1a	400 mg	392 mg	0.33:1	0.17:1 (1st), 0.33:1 (2nd), 0.50:1 (3rd)	(<i>R</i>)- 2a	91	98	(<i>S</i>)- 1a	3	nd	3a 6

[a] The amount of the filler was selected to adjust the residence time to 30 min. [b] Molar ratio [%] of the compounds (R)-**2**, (S)-**1**, and **3** was determined by ¹H NMR analysis of the crude product obtained from 2 mL of the eluent collected after the system had reached a steady state. [c] Optical purity was determined by HPLC using a chiral column, Daicel CHIRALPAK AD-3 (4.6 mm × 250 mm). Nd: not determined. [d] The ratio was calculated on the basis of the alcohol moiety and corresponded to half this quantity based on the molar amount. [e] Similarly to the typical procedure for the preparation of (R)-**2a** shown in the experimental section, a reactor was prepared using the following materials: 1st column; CALB (400 mg), VMPS4 (68 mg), and DualPore silica (160 mg); 2nd column; CALB (400 mg), VMPS4 (132 mg), and DualPore silica (132 mg); 3rd column; CALB (400 mg), VMPS4 (200 mg), and DualPore silica (100 mg), which were connected in series. A solution of (±)-**1a** (89 mg, 0.60 mmol), vinyl acetate (0.22 mL, 2.4 mmol) in dry MeCN (6.0 mL) was pumped through the reactor at a flow rate of 0.12 mL/min (residence time: 30 min) using a syringe pump. A whole eluent was collected and subjected to ¹H NMR and chiral HPLC analyses.

reactor (Table 3, entries 2 and 3), and the optical purity of recovered (*S*)-**1b** was higher, that is, the racemization of (*S*)-**1b** was less efficient, than that listed in Table 3, entry 6. A similar flow DKR of (\pm)-**1a** using a column reactor with a ratio gradient of CALB and VMPS4 significantly decreased the amount of **3a** and thereby improved the yield of (*R*)-**2a** compared to that using a single layer reactor (entries 9 and 10). The flow DKR using a similar reactor with four times amount of each material, CALB (1.20 g), VMPS4 (0.40 g), and DualPoreTM silica (0.39 g), was conducted at the flow rate of 0.12 mL/min (residence time: 30 min) to produce similar results, 91 % ¹H NMR molar ratio of (*R*)-**2a** (98 % ee) (entry 11) (for the details of the flow DKR of **1a**, see Supporting Information). These studies demonstrate an increased efficiency of the column reactor, when containing two different catalysts, with a suitable catalyst-ratio gradient for the continuous-flow DKR.

Based on the above results, a range of secondary alcohols (\pm)-**1a–1f** (0.60 mmol) were applied for continuous-flow DKR using the three-layered column reactor packed with a gradient ratio of VMPS4 and CALB. The alcohols include aromatic allylic alcohols **1a–1c**, aliphatic dienol **1d**, benzylic alcohol **1e**, and propargylic alcohol **1f**. After optimization of the ratio of VMPS4 to CALB for each substrate (\pm)-**1a–1f** (for details, see Supporting Information), the corresponding esters (*R*)-**2a–2f** were obtained in 88–92 % isolated yield with 96–99 % ee (Table 4). In most cases, the alcohols were consumed within a residence time of 30 min.

The flow DKR of (\pm)-**1a** was continuously conducted for 3 days (Figure 1). In this case, the addition of two layers comprising CALB alone before and after the three-layered gradient catalysts containing VMPS4 and CALB resulted in a slight improvement in the conversion (a comparison with the DKR using a three-layered column as well as the time course of these two reactions are shown in the Supporting Information). Thus, the use of 0.50 g of CALB and 0.10 g (20 μ mol, 0.16 mol %) of VMPS4 was sufficient to convert (\pm)-**1a** (1.82 g, 12.3 mmol) into (*R*)-**2a** (2.13 g, 11.2 mmol) in 91 % isolated yield and with 99% ee. In our previous batch system, 100 mg of CALB and 17 mg (0.50 mol %) of VMPS4 were used to convert 100 mg of (\pm)-**1a** to optically pure (*R*)-**2a** (98 % isolated yield).^[10d] Therefore, the amount of CALB per 1 gram of **1a** used in the abovementioned 3-day continuous flow DKR was reduced to less than 1:10 of the batch reaction and that of VMPS4 was about 1:3 (for a detailed comparison, see Supporting Information). These facts exhibit the higher turnover numbers of each catalyst in the continuous-flow DKR reactions compared to those of the batch reactions.

Table 4. Continuous-flow DKR of secondary alcohols (\pm)-**1a–1f**.

 <i>(R)</i> - 2a 88%, 99% ee 2:91:7	 <i>(R)</i> - 2b 92%, 98% ee <1:92:8	 <i>(R)</i> - 2c 91%, 99% ee <1:92:8
 <i>(R)</i> - 2d 92%, 96% ee <1:92:8	 <i>(R)</i> - 2e ^[c] 88%, 99% ee 2:91:7	 <i>(R)</i> - 2f ^[d] 92%, 99% ee 5:94:1

[a] The w/w ratios of VMPS4/CALB were 0.33:1 for **2a**, 0.10:1 for **2b**, 0.14:1 for **2c–2e**, and 0.50:1 for **2f**. The amount of DualPore silica was selected to obtain a residence time of 30 min. The amounts of VMPS4 and DualPore silica in each layer are listed in the Experimental Section. [b] The values below each compound number present the isolated yield and optical purity of (*R*)-**2** and the ¹H NMR molar ratio of **1**, **2**, and **3** of the crude product. [c] Flow rate: 0.015 mL/min and residence time: 60 min. [d] Using vinyl butyrate instead of vinyl acetate.

Conclusions

We achieved the continuous-flow DKR of various secondary alcohols to give the corresponding esters in 88–92 % isolated yields and with 96–99 % ee. Our DKR method features the use of a column reactor packed with a mixture of two solid catalysts, that is, CALB (commercial *Candida antarctica* lipase B immobilized on an acrylic resin) and VMPS4 (oxovanadium species immobilized on inner surface of mesoporous silica). Their high compatibility is one of the major advantages because the catalysts can be mixed without any special care and their catalytic activity is maintained for days. However, the large difference in the particle size of these two catalysts resulted in the loss of the initial homogeneous distribution in the column reactor. This is due to a move of small particles when pumping the solution through the reactor and resulted in a decreased efficacy of the

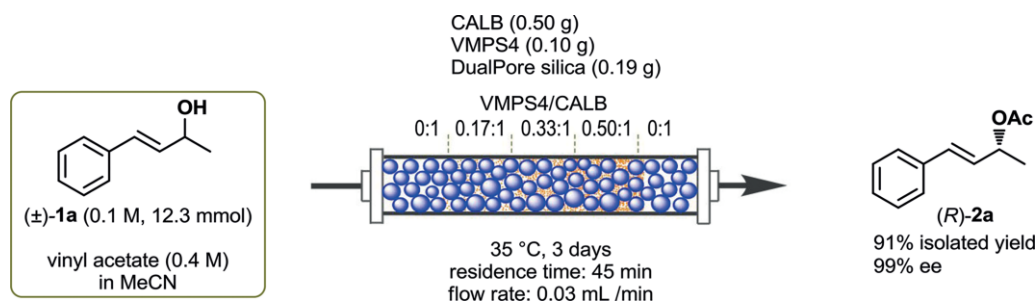


Figure 1. Continuous-flow DKR of (\pm)-**1a** over 3 days using a five-layered packed column.

collaborative DKR process. Another critical issue affecting our continuous flow DKR process was the formation of side products, in detail dimeric ethers, which hardly occurred in the batch method. The formation of these side products was probably caused by an increased catalyst concentration compared to the batch reactions. The former problem was overcome by using DualPore™ silica beads as a filler, resulting in the maintenance of the initial distribution of the individual catalysts. The latter problem was solved by a packing method in which the mixing ratio of the two catalysts was changed in a stepwise fashion. The use of DualPore™ silica beads also enabled the latter packing method. Due to these improvements, the flow DKR could be conducted for continuous 3 days to produce the desired esters in high yield and with 99% ee by using smaller amounts of CALB and VMPS4 compared to the corresponding batch reactions. Considering the increasing need and importance of continuous-flow reactions,^[1–3,7,9b,11,17] this study should provide useful information for continuous-flow systems using a column reactor packed with multiple catalysts where several different reactions proceed simultaneously.

One of the well-known advantages of flow reactions is their easy scale up while maintaining their efficiency. In this study, an increased production per hour was proven by a preliminary study using a reactor with a four fold amount of each catalyst and filler at a four fold flow rate (Table 3, entries 10 and 11). Therefore, we believe that our method can be applied to further scale-up production by enlargement of the reactor as well as its numbering-up.

Further studies on the improvement of our continuous-flow DKR process using a column reactor with a combination of immobilized enzymes and immobilized racemization catalysts and its application to a wider range of substrates are currently ongoing in our laboratories.

Experimental Section

General considerations

Infrared (IR) absorption spectra were recorded on a SHIMADZU FTIR-8400S spectrophotometer. ¹H and ¹³C NMR spectra were measured on JEOL JNM-ECA500 (¹H: 500 MHz, ¹³C: 125 MHz) and JEOL JNM-ECS400 (¹H: 400 MHz, ¹³C: 100 MHz) instruments. Chemical shifts of ¹H and ¹³C NMR spectra are reported in δ (ppm) relative to the residual nondeuterated solvent signal for ¹H (CHCl₃: δ = 7.26 ppm) and relative to the solvent signal for ¹³C (CDCl₃: δ = 77.0 ppm). The mass spectra (MS) were measured on JEOL JMS-S3000 (MALDI). HPLC analyses were carried out using a JASCO LC-2000Plus system (HPLC pump: PU-2080, UV detector: MD-2018) equipped with Daicel CHIRALPAK AD-3 with a size of 4.6 mm × 250 mm. Optical rotations were measured on a JASCO P-1020 polarimeter.

Candida antarctica lipase B (CALB) immobilized on an acrylic resin (commercial name: Novozym 435 or Chirazyme L-2 C4) was purchased from Roche Diagnostics K. K., Japan and was used as received without further purification. VMPS4 (vanadium content: 0.2 mmol/g) was prepared according to the reported method^[10d] (it is now commercially available from FUJIFILM Wako Pure Chemical Corp., Japan). DualPore™ silica beads (particle size: 0.020–0.063 mm, density: 0.16 g/mL) consist of micro-sized through-pores (pore size 0.5–1 μ m) and nanosized pores (pore size 20 nm), available from DPS Inc., was used as received without further purification.

Silica gel 60N purchased from Kanto Chemical Co., Inc., Japan was used for column chromatography. All reagents were of reagent grade. In general, the reactions were carried out in commercial anhydrous solvents.

Equipment for Continuous-Flow DKR

An Omnifit® EZ SolventPlus™ column complete AF set (inner diameter 6.6 mm, total length 100 mm) with an adjustable endpiece and a fixed endpiece, purchased from Diba Industries Inc., USA, was used as a reactor for the flow DKR. A polytetrafluoroethylene (PTFE) tube (outer diameter 1/16", inner diameter 1/32"), dual syringe pumps (Catamaran HII-10), purchased from Techno Applications Co., Ltd., Japan, and an incubator CN-25A, purchased from Mitsubishi Electric Engineering Co., Ltd., Japan, were used.

Preparation of Racemic Alcohols 1

The known alcohols [(±)-**1a**,^[10f] (±)-**1b**,^[10f] (±)-**1d**,^[10f] (±)-**1e**,^[10e] and (±)-**1f**^[10a]] were prepared according to the reported methods, and (±)-**1c** was prepared as follows.

(E)-4-(3,4,5-Trimethoxyphenyl)but-3-en-2-ol [(±)-1c]: Under an argon atmosphere, MeLi (a 1.16 M solution in Et₂O, 6.6 mL, 7.6 mmol) was added to a solution of (E)-3-(3,4,5-trimethoxyphenyl)prop-2-enal^[18] (1.53 g, 6.9 mmol) in THF (30 mL) at –78 °C. The reaction mixture was warmed to room temperature and stirred for 10 h. After the reaction was quenched with sat. aq. NH₄Cl at 0 °C, the organic materials were extracted with EtOAc three times. The combined organic extract was washed with brine, dried with MgSO₄, and the solvents evaporated in vacuo. The residue was purified by column chromatography (CH₂Cl₂/EtOAc = 9:1) to afford (±)-**1c** (1.58 g, 96 % yield) as a slight yellow oil. ¹H NMR data of the obtained (±)-**1c** was in good agreement with those reported in the literature.^[19]

A typical procedure for continuous-flow DKR of (±)-1 using a column reactor with a ratio gradient of CALB and VMPS4 in three layers (Table 4).

(R,E)-4-Phenyl-3-buten-2-yl acetate [(R)-2a] (The results of the reaction condition optimization of the flow DKR of (±)-**1a** are shown in Table S2 in Supporting Information, and its entry 5 was selected as an experiment with the best conditions).

An Omnifit® EZ SolventPlus™ column, its adjustable endpiece, a PTFE tube, two 12-mL syringes, and three 12-mL screw cap tubes were vacuum-dried and filled with argon. The first-layer materials for the column reactor [CALB (100 mg), VMPS4 (17 mg), and DualPore silica (40 mg)] were well mixed in a screw cap tube and filled with argon. The second-layer materials [CALB (100 mg), VMPS4 (33 mg), and DualPore silica (33 mg)] and the third-layer ones [CALB (100 mg), VMPS4 (50 mg), DualPore silica (25 mg)] were placed in separate tubes, mixed well, and filled with argon. The first-layer materials were poured into the reactor (Cautions: This operation was conducted in front of a static eliminator to prevent from sticking particles to the tube or reactor wall. Tapping of the reactor is not recommended because the homogeneity of the materials gets lost). In a similar way, the second-layer materials and the third-layer materials were placed in the reactor sequentially, and the adjustable endpiece was fastened to fix the packed layers. PTFE tubes were connected to the reactor, which was placed in an incubator at 35 °C and washed with dry MeCN (10 mL) at a flow rate of 0.10 mL/min using a syringe pump. A solution of (±)-**1a** (89 mg, 0.60 mmol), vinyl acetate (0.22 mL, 2.4 mmol) in dry MeCN (6.0 mL) was pumped through the reactor at a flow rate of 0.03 mL/min using a syringe pump. After pumping the whole solution, another solution of vinyl acetate (0.073 mL, 0.80 mmol) in dry MeCN (2 mL) was immediately

pumped at a flow rate of 0.03 mL/min to wash out the compounds remaining in the reactor. The whole eluent was concentrated in vacuo. ¹H NMR analysis of the residue showed that the molar ratio of **1a**, **2a**, and **3a** was 2:91:7. The residue was purified by SiO₂ column chromatography (hexanes/EtOAc = 20:1) to give (*R*)-**2a** (100 mg, 88 % yield, 99 % ee) as a colorless oil. The spectroscopic data of the obtained product (*R*)-**2a** was in good agreement with those reported in our previous paper.^[10f] Its optical purity was determined by HPLC analysis at 20 °C using a Daicel CHIRALPAK AD-3 column (hexanes/2-propanol = 99:1, 1.0 mL/min, UV detection: 248 nm, retention times: 6.3 (*R*), 7.5 min (*S*)). [α]_D²¹ = +149.5 (c 1.0, CHCl₃) (lit.^[10f] [α]_D²⁵ = +144.5 (c 1.00, CHCl₃) for 98 % ee, lit.^[20] [α]_D²¹ = +120.2 (c 1.14, CHCl₃) for 94 % ee).

(*R,E*)-4-(4-Methoxyphenyl)-3-buten-2-yl acetate [(*R*)-**2b**]

Similarly to the preparation of (*R*)-**2a**, (*R*)-**2b** (122 mg, 92 % yield, 98 % ee) was obtained from (±)-**1b** (107 mg, 0.60 mmol) using the reactor made of the following materials: 1st layer; CALB (100 mg), VMPS4 (6 mg), and DualPore silica (47 mg); 2nd layer; CALB (100 mg), VMPS4 (10 mg), and DualPore silica (45 mg); 3rd layer; CALB (100 mg), VMPS4 (14 mg), and DualPore silica (43 mg). The product (*R*)-**2b** was obtained as a colorless oil. [α]_D²¹ = +139.4 (c 1.0, CHCl₃) (lit.^[10f] [α]_D²⁵ = +125.9 (c 1.10, CHCl₃) for >99 % ee, lit.^[21] [α]_D²⁵ = +137.8 (c 1.1, CHCl₃) for 98.9 % ee). The spectroscopic data of the obtained product (*R*)-**2b** were in good agreement with those reported in our previous paper.^[10f] Its optical purity was determined by HPLC analysis at 20 °C using a Daicel CHIRALPAK AD-3 column (hexanes/2-propanol = 99:1, 1.0 mL/min, UV detection: 263 nm, retention times: 9.4 (*R*), 11.3 min (*S*)).

(*R,E*)-4-(3,4,5-Trimethoxyphenyl)-3-buten-2-yl acetate [(*R*)-2c**]** (The results of the reaction condition optimization of flow DKR of (±)-**1c** are shown in Table S3, and its entry 3 was selected as an experiment with the best conditions).

Similarly to the preparation of (*R*)-**2a**, (*R*)-**2c** (153 mg, 91 % yield, 99 % ee) was obtained from (±)-**1c** (143 mg, 0.60 mmol) using the reactor made of the following materials: 1st layer; CALB (100 mg), VMPS4 (7 mg), and DualPore silica (47 mg); 2nd layer; CALB (100 mg), VMPS4 (14 mg), and DualPore silica (43 mg); 3rd layer; CALB (100 mg), VMPS4 (22 mg), and DualPore silica (39 mg). The product (*R*)-**2c** was obtained as a slight yellow oil. [α]_D²² = +110.1 (c 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ = 1.41 (d, *J* = 6.5 Hz, 3H), 2.08 (s, 3H), 3.84 (s, 3H), 3.87 (s, 6H), 5.51 (m, 1H), 6.10 (dd, *J* = 16.0, 6.5 Hz, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.60 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 20.31, 21.35, 55.98, 60.85, 70.88, 103.47, 128.18, 131.56, 131.94, 137.91, 153.20, 170.30. IR (neat): $\tilde{\nu}$ = 1736 cm⁻¹. HRMS (ESI) *m/z* calcd. for C₁₅H₂₀O₅ [M]⁺: 280.1311, found 280.1305. Its optical purity was determined by HPLC analysis at 20 °C using a Daicel CHIRALPAK AD-3 column (hexanes/2-propanol = 90:10, 1.0 mL/min, UV detection: 223 nm, retention times: 8.9 (*R*), 10.0 min (*S*)).

(*R,E*)-4-(1-Cyclohexen-1-yl)-3-buten-2-yl acetate [(*R*)-2d**]** (The results of the reaction condition optimization of flow DKR of (±)-**1d** are shown in Table S4, and its entry 4 was selected as an experiment with the best conditions).

Similarly to the preparation of (*R*)-**2a**, (*R*)-**2d** (106 mg, 92 % yield, 96 % ee) was obtained from (±)-**1d** (91 mg, 0.60 mmol) using the reactor made of the following materials: 1st layer; CALB (100 mg), VMPS4 (7 mg), and DualPore silica (47 mg); 2nd layer; CALB (100 mg), VMPS4 (14 mg), and DualPore silica (43 mg); 3rd layer; CALB (100 mg), VMPS4 (22 mg), and DualPore silica (39 mg). The product (*R*)-**2d** was obtained as a colorless oil. [α]_D²² = +87.5 (c 1.0, CHCl₃) (lit.^[10f] [α]_D²⁴ = +72.7 (c 1.18, CHCl₃) for 92 % ee). The spectroscopic data of the obtained product (*R*)-**2d** were in good agreement

with those reported in our previous paper.^[10f] Its optical purity was determined by HPLC analysis at 20 °C using a Daicel CHIRALPAK AD-3 column (hexanes/2-propanol = 99.5:0.5, 1.0 mL/min, UV detection: 233 nm, retention times: 5.7 (*R*), 6.8 min (*S*)).

(*R*)-1-(4-Methoxyphenyl)ethyl acetate [(*R*)-2e**]** (The results of the reaction condition optimization of flow DKR of (±)-**1e** are shown in Table S5, and its entry 6 was selected as an experiment with the best conditions).

Similarly to the preparation of (*R*)-**2a**, (*R*)-**2e** (103 mg, 88 % yield, 99 % ee) was obtained from (±)-**1e** (91 mg, 0.60 mmol) using the reactor made of the following materials: 1st layer; CALB (100 mg), VMPS4 (7 mg), DualPore silica (47 mg); 2nd layer; CALB (100 mg), VMPS4 (14 mg), and DualPore silica (43 mg); 3rd layer; CALB (100 mg), VMPS4 (22 mg), and DualPore silica (39 mg). Flow rate was changed into 0.015 mL/min. The product (*R*)-**2e** was obtained as a colorless oil. [α]_D²² = +127.6 (c 1.0, CHCl₃) (lit.^[10e] [α]_D^{26.5} = +121.7 (c 1.00, CHCl₃) for 99 % ee). The spectroscopic data of the obtained product (*R*)-**2e** was in good agreement with those reported in our previous paper.^[10e] Its optical purity was determined by HPLC analysis at 20 °C using a Daicel CHIRALPAK AD-3 column (hexanes/2-propanol = 99:1, 1.0 mL/min, UV detection: 225 nm, retention times: 7.4 (*R*), 14.1 min (*S*)).

(*R*)-1-(Thiophen-2-yl)prop-2-yn-1-yl butyrate [(*R*)-2f**]** (The results of the reaction condition optimization of flow DKR of (±)-**1f** are shown in Table S6, and its entry 5 was selected as an experiment with the best conditions).

Similarly to the preparation of (*R*)-**2a**, (*R*)-**2f** (115 mg, 92 % yield, 99 % ee) was obtained from (±)-**1f** (83 mg, 0.60 mmol) and vinyl butyrate (0.31 mL, 2.4 mmol) using the reactor made of the following materials: 1st layer; CALB (100 mg), VMPS4 (33 mg), and DualPore silica (33 mg); 2nd layer; CALB (100 mg), VMPS4 (50 mg), and DualPore silica (25 mg); 3rd layer; CALB (100 mg), VMPS4 (67 mg), and DualPore silica (17 mg). The product (*R*)-**2f** was obtained as a yellow oil. [α]_D²² = +30.7 (c 1.0, CHCl₃) (lit.^[10a] [α]_D²² = +28.0 (c 0.82, CHCl₃) for 98 % ee). The spectroscopic data of the obtained product (*R*)-**2f** was in good agreement with those reported in our previous paper.^[10a] Its optical purity was determined by HPLC analysis at 20 °C using a Daicel CHIRALPAK AD-3 column (hexanes/2-propanol = 99:1, 1.0 mL/min, UV detection: 235 nm, retention times: 6.8 (*R*), 7.4 min (*S*)).

Continuous-Flow DKR of (±)-**1a** over 3 Days Using a Five-Layered Packed Column.

Similarly to the preparation of (*R*)-**2a**, a reactor was prepared using the following materials: 1st layer; CALB (100 mg) and DualPore silica (40 mg); 2nd layer; CALB (100 mg), VMPS4 (17 mg), and DualPore silica (40 mg); 3rd layer CALB (100 mg), VMPS4 (33 mg), and DualPore silica (33 mg); 4th layer CALB (100 mg), VMPS4 (50 mg), and DualPore silica (25 mg); and 5th layer CALB (100 mg) and DualPore silica (40 mg). A solution of (±)-**1a** (1.82 g, 12.3 mmol), vinyl acetate (4.6 mL, 49 mmol) in MeCN (123 mL) was continuously pumped through the reaction column at a flow rate of 0.03 mL/min at 35 °C. The whole solution was pumped into the reactor over 3 days, and then another solution of vinyl acetate (0.073 mL, 0.80 mmol) in dry MeCN (2 mL) was immediately pumped at a flow rate of 0.03 mL/min to wash out the compounds remaining in the reactor. The eluent was collected in a flask every 12 hours, and the 6th fraction and the washout solution were collected in the 6th flask. Each fraction was concentrated in vacuo, and the residue was subjected to ¹H NMR and chiral HPLC analyses to determine the molar ratio of (*S*)-**1a**, (*R*)-**2a**, and **3a** and the optical purity of (*S*)-**1a** and (*R*)-**2a** (see Figure S2 in Supporting Information). All fractions were combined

and purified by column chromatography (EtOAc/hexane = 1:10) to afford (*R*)-**2a** (2.13 g, 91 % yield, 99 % ee).

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- [1] For recent reviews, see a) P. Brandão, M. Pineiro, T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2019**, 2019, 7188–7217; b) A. Nagaki, *Tetrahedron Lett.* **2019**, 60, 150923; c) S. Santoro, F. Ferlin, L. Ackermann, L. Vaccaro, *Chem. Soc. Rev.* **2019**, 48, 2767–2782; d) A. R. Bogdan, A. W. Dombrowski, *J. Med. Chem.* **2019**, 62, 6422–6468; e) M. P. Thompson, I. Peñafliel, S. C. Cosgrove, N. J. Turner, *Org. Process Res. Dev.* **2019**, 23, 9–18; f) F. M. Akwi, P. Watts, *Chem. Commun.* **2018**, 54, 13894–13928; g) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, 45, 4892–4928; h) I. Eş, J. D. G. Vieira, A. C. Amaral, *Appl. Microbiol. Biotechnol.* **2015**, 99, 2065–2082; i) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, 54, 6688–6728; *Angew. Chem.* **2015**, 127, 6788–6832; j) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, 78, 6384–6389; k) N. G. Anderson, *Org. Process Res. Dev.* **2012**, 16, 852–869.
- [2] a) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, 47, 4583–4592; b) R. Yuryev, S. Strompen, A. Liese, *Beilstein J. Org. Chem.* **2011**, 7, 1449–1467; c) C. G. Frost, L. Mutton, *Green Chem.* **2010**, 12, 1687–1703.
- [3] a) M. Santi, J. Seitz, R. Cicala, T. Hardwick, N. Ahmed, T. Wirth, *Chem. Eur. J.* **2019**, 25, 16230–16235; b) D. E. Fitzpatrick, T. Maujean, A. C. Evans, S. V. Ley, *Angew. Chem. Int. Ed.* **2018**, 57, 15128–15132; *Angew. Chem.* **2018**, 130, 15348–15352.
- [4] For recent reviews on lipase-catalyzed DKR, see a) S. Akai, in *Future Directions in Biocatalysis* (2nd ed.) (Ed. T. Matsuda), Elsevier Science, Amsterdam, **2017**, pp. 337–358; b) Z. S. Seddigi, M. S. Malik, S. A. Ahmed, A. O. Babalghith, A. Kamal, *Coord. Chem. Rev.* **2017**, 348, 54–70; c) O. Verho, J. E. Bäckvall, *J. Am. Chem. Soc.* **2015**, 137, 3996–4009; d) S. Takizawa, H. Gröger, H. Sasai, *Chem. Eur. J.* **2015**, 21, 8992–8997; e) A. S. de Miranda, L. S. M. Miranda, R. O. M. A. de Souza, *Biotechnol. Adv.* **2015**, 33, 372–393; f) S. Akai, *Chem. Lett.* **2014**, 43, 746–754.
- [5] Recent papers: a) G. A. I. Moustafa, Y. Oki, S. Akai, *Angew. Chem. Int. Ed.* **2018**, 57, 10278–10282; *Angew. Chem.* **2018**, 130, 10435–10439; b) K. P. J. Gustafson, A. Guðmundsson, K. Lewis, J. E. Bäckvall, *Chem. Eur. J.* **2017**, 23, 1048–1051; c) Q. Yang, N. Zhang, M. Liu, S. Zhou, *Tetrahedron Lett.* **2017**, 58, 2487–2489; d) O. El-Sepelgy, N. Alandini, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, 55, 13602–13605; *Angew. Chem.* **2016**, 128, 13800–13803; e) C. L. Pollock, K. J. Fox, S. D. Lacroix, J. McDonagh, P. C. Marr, A. M. Nethercott, A. Pennycook, S. Qian, L. Robinson, G. C. Saunders, A. C. Marr, *Dalton Trans.* **2012**, 41, 13423–13428.
- [6] A. Berkessel, M. L. Sebastian-Ibarz, T. N. Müller, *Angew. Chem. Int. Ed.* **2006**, 45, 6567–6570; *Angew. Chem.* **2006**, 118, 6717–6720.
- [7] a) A. da S. de França, M. V. M. Silva, R. V. Neves, S. P. de Souza, R. A. C. Leão, C. M. Monteiro, A. Rocha, C. A. M. Afonso, R. O. M. A. de Souza, *Bioorg. Med. Chem.* **2018**, 26, 1333–1337; b) A. S. de Miranda, M. V. M. de Silva, F. C. Dias, S. P. de Souza, R. A. C. Leão, R. O. M. A. de Souza, *React. Chem. Eng.* **2017**, 2, 375–381; c) L. Poppe, A. Tomin, Z. Boros, E. Varga, L. Uerge, F. Darvas, *Hung. Pat. Appl. HU 2009000720*; *Chem. Abstr.* **2012**, 156, 99018; d) S. Wuyts, J. Wahlen, P. A. Jacobs, D. E. De Vos, *Green Chem.* **2007**, 9, 1104–1108.
- [8] P. Ödman, L. A. Wessjohann, U. T. Bornscheuer, *J. Org. Chem.* **2005**, 70, 9551–9555.
- [9] a) R. Nieguth, J. Ten Dam, A. Petrenz, A. Ramanathan, U. Hanefeld, M. B. Ansorge-Schumacher, *RSC Adv.* **2014**, 4, 45495–45503; b) Z. Wang, X. Li, W. Wang, Y. Tang, Y. Zhang, *J. Catal.* **2013**, 300, 1–8; c) P. Lozano, T. de Diego, C. Mira, K. Montague, M. Vaultier, J. L. Iborra, *Green Chem.* **2009**, 11, 538–542; d) Y. Zhu, K. L. Fow, G. K. Chuah, S. Jaenicke, *Chem. Eur. J.* **2007**, 13, 541–547; e) P. Lozano, T. de Diego, M. Larnicol, M. Vaultier, J. L. Iborra, *Biotechnol. Lett.* **2006**, 28, 1559–1565.
- [10] a) S. Kawanishi, S. Oki, D. Kundu, S. Akai, *Org. Lett.* **2019**, 21, 2978–2982; b) K. Sugiyama, S. Kawanishi, Y. Oki, M. Kamiya, R. Hanada, M. Egi, S. Akai, *Bioorg. Med. Chem.* **2018**, 26, 1378–1386; c) S. Kawanishi, K. Sugiyama, Y. Oki, T. Ikawa, S. Akai, *Green Chem.* **2017**, 19, 411–417; d) K. Sugiyama, Y. Oki, S. Kawanishi, K. Kato, T. Ikawa, M. Egi, S. Akai, *Catal. Sci. Technol.* **2016**, 6, 5023–5030; e) M. Egi, K. Sugiyama, M. Saneto, R. Hanada, K. Kato, S. Akai, *Angew. Chem. Int. Ed.* **2013**, 52, 3654–3658; *Angew. Chem.* **2013**, 125, 3742–3746; f) S. Akai, R. Hanada, N. Fujiwara, Y. Kita, M. Egi, *Org. Lett.* **2010**, 12, 4900–4903; g) S. Akai, K. Tanimoto, Y. Kanao, M. Egi, T. Yamamoto, Y. Kita, *Angew. Chem. Int. Ed.* **2006**, 45, 2592–2595; *Angew. Chem.* **2006**, 118, 2654–2657.
- [11] For recent papers and a review on the continuous-flow KR of racemic secondary alcohols using reactors packed with lipases, see a) A. Todea, P. Borza, A. Cimporescu, C. Paul, F. Peter, *Catal. Today* **2018**, 306, 223–232; b) M. V. M. Silva, J. F. Bassut, I. I. Junior, S. P. de Souza, M. L. G. Estrada, L. S. M. Miranda, R. O. M. A. de Souza, *RSC Adv.* **2015**, 5, 102409–102415; c) I. Itabaiana, L. S. de Mariz, E. Miranda, R. O. M. A. de Souza, *J. Mol. Catal. B* **2013**, 85–86, 1–9.
- [12] An Omnifit EZ SolventPlus™ column complete AF set (inner diameter 6.6 mm, column length 100 mm) with an adjustable endpiece, purchased from Diba Industries Inc., USA, was used.
- [13] The residence time was measured by watching the flow of a solvent flushing dry material(s) packed in a reactor.
- [14] The *E* value indicates the enantioselectivity in an enzymatic KR [C. S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.* **1982**, 104, 7294–7299] and is the same as the *S* value generally used to denote the enantioselectivity in the organocatalytic KR [J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, 343, 5–26].
- [15] The DualPore™ silica beads consist of micro-sized through-pores (pore size 0.5–1 µm), which are intricately pierced through the silica particles, and nanosized pores (pore size 20 nm). They are available from DPS Inc. (<https://www.dps-inc.co.jp/en/t-dp/>).
- [16] Although the formation of the water elimination products, such as styrene, as other side products was reported in oxovanadium-catalyzed DKR and racemization,^[7] we found that the formation of these products was below the detection limit based on ¹H NMR analysis of crude products (for ¹H NMR data, see Supporting Information). The difference is probably attributed to the reaction temperature—DKR and racemization using VOSO₄·*n*H₂O were conducted at 70–80 °C,^[7] and DKR using VMPS4 in this study was run at 35 °C.
- [17] A related chemoenzymatic continuous-flow DKR of secondary amines, see: E. Farkas, M. Oláh, A. Földi, J. Kóti, J. Éles, J. Nagy, C. A. Gal, C. Paizs, G. Hornyánszky, L. Poppe, *Org. Lett.* **2018**, 20, 8052–8056.
- [18] R. Labruère, B. Gautier, M. Testud, J. Seguin, C. Lenoir, S. Desbène-Finck, P. Helissey, C. Garbay, G. G. Chabot, M. Vidal, S. Giorgi-Renault, *ChemMedChem* **2010**, 5, 2016–2025.
- [19] S.-R. Guo, Y.-Q. Yuan, *Synlett* **2015**, 26, 1961–1968.
- [20] a) J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio, P. S. Baran, *J. Am. Chem. Soc.* **2008**, 130, 17938–17954; b) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2009**, 48, 2854–2867; *Angew. Chem.* **2009**, 121, 2896–2910.
- [21] J. H. Choi, Y. K. Choi, Y. H. Kim, E. S. Park, E. J. Kim, M.-J. Kim, J. Park, *J. Org. Chem.* **2004**, 69, 1972–1977.

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